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Academia–Pharma Intersect: Genitourinary Cancer: Prostate

Castration-Resistant Prostate Cancer: Targeted Therapies and Individualized Treatment

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The article describes a series of drugs that are in development for prostate cancer and, as such, are, by definition, investigational.

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ABSTRACT

Various molecular mechanisms have been implicated in the progression from hormone-sensitive to castration-resistant prostate cancer (CRPC). Novel targeted agents to treat CRPC have been developed that inhibit either androgen receptor (AR)-mediated signaling (AR antagonists and inhibitors of androgen synthesis) or non–AR-mediated signaling (inhibitors of Src, mammalian target of rapamycin, chaperone proteins, insulin-like growth factor-1 receptor, vascular endothelial growth factor, and endothelin-A receptor) pathways. However, variable efficacy has been observed in clinical trials, most likely because of the biologic heterogeneity of CRPC. To account for potential differences in disease biology, a more individualized approach to treatment, based on genomic and/or proteomic analyses of individual tumors, is being investigated. By identifying tumors with a characteristic molecular subtype and assigning treatment accordingly, it is hoped that a higher proportion of patients will benefit from targeted therapy. Additionally, lessons learned through the application of these technologies to prostate cancer may subsequently influence therapeutic development in other solid tumors. ***The Oncologist*** 2011;16:264–275

INTRODUCTION

Although most men who develop prostate cancer do not die from their disease, those who develop castration-resistant prostate cancer (CRPC) have a poor prognosis and are more likely to die from complications of metastatic disease than from comorbid illness. Approved systemic chemotherapies for CRPC provide limited benefits. Docetaxel, a taxane inhibitor of microtubule function, remains the standard first-line treatment based on two phase III trials that showed a median survival time of 18–19 months [1, 2]. Efforts are ongoing to develop various therapies targeting mechanisms behind tumor progression.

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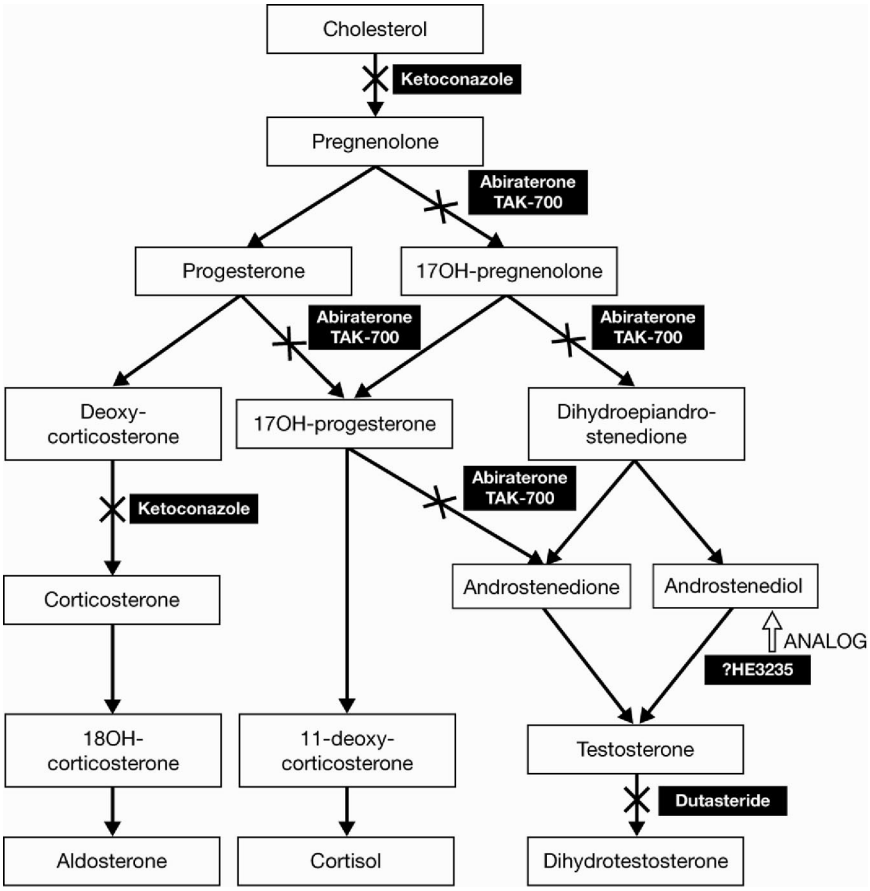

Figure 1. The androgen synthesis pathway and actions of inhibitors.

Several molecular pathways have been implicated in prostate cancer progression from localized disease that remains sensitive to androgen deprivation to CRPC, the lethal tumor phenotype. Pathways can be divided into those mediated by the androgen receptor (AR) and those without direct agonism of the AR [3]. Novel therapies have been rationally designed to target molecular pathways involved in oncogenesis and disease progression although results from trials have been mixed. The biologic heterogeneity of CRPC, including potential involvement of AR-mediated or AR-independent pathways, is a probable cause of the variable responses seen with targeted therapies. Arguably, a more rational approach could involve determining the biologic status of an individual tumor before therapy by assessing gene expression, hormone metabolism, or signaling activity, and directing treatment accordingly. This more individualized approach is being tested in early-phase clinical trials.

Here, we highlight several novel therapies for CRPC targeted to AR-mediated or non–AR-mediated pathways that have recently entered clinical trials, including the molecular rationale and available clinical data. We also summarize emerging evidence on the potential of individualized therapy for CRPC.

Targeting AR-Mediated Signaling

Numerous lines of evidence indicate that persistent AR activation is an important mediator of disease progression in CRPC [3, 4]. Proposed mechanisms include: *AR* gene amplification or overexpression; *AR* gene mutation leading to promiscuous ligand/cofactor interaction; enhanced AR signal transduction mediated via coactivators; and endocrine or autocrine activation of the AR, for example, by adrenal androgens or intratumoral production of dihydrotestosterone (DHT). Established AR-directed approaches include AR antagonists, for example, bicalutamide and flutamide, in addition to agents that block the production of AR-activating hormones, for example, ketoconazole (Fig. 1). However, in patients with AR overexpression, traditional AR antagonists have shown agonistic activity toward the AR [5], which may explain prostate-specific antigen (PSA) decreases that sometimes occur following antiandrogen withdrawal [6, 7] and the limited additive effects of

antiandrogens combined with luteinizing hormone-releasing hormone–based therapies [8].

MDV3100 is a novel orally available AR antagonist with no known agonistic activity that was discovered through compound screening in a cellular model of prostate cancer activated by AR overexpression [9]. In a phase I/II trial, 140 patients with progressive CRPC were treated with doses in the range of 30–600 mg/day. In the chemotherapy-naïve and postchemotherapy subgroups, respectively, a 50% PSA decline from baseline occurred in 62% and 51%, a partial response (PR) in soft-tissue tumors evaluable by the Response Evaluation Criteria in Solid Tumors (RECIST) was achieved in 36% and 12%, stabilized bone disease at 12 weeks on bone scan occurred in 63% and 51%, and the median time to radiologic progression was not reached and 29 weeks (47 weeks in all patients) [10]. A randomized, placebo-controlled phase III study of MDV3100 monotherapy versus placebo in patients with docetaxel-pretreated CRPC has completed accrual; a second phase III study of MDV3100 monotherapy versus placebo in chemotherapy-naïve patients with CRPC has recently opened (Table 1).

Therapies that decrease androgen production from both endocrine and autocrine sources are also being developed. Abiraterone acetate is a selective and irreversible inhibitor of cytochrome P450 (CYP450)c17, an enzyme involved in androgen synthesis from both adrenal and other sources. Encouraging activity and safety with abiraterone were seen in phase I studies [11, 12]. In a phase II trial of 47 patients with CRPC with prior docetaxel therapy, 50% PSA declines were achieved with abiraterone in 51% of patients, and among the 30 patients who had RECIST-evaluable tumors, 27% had a PR [13]. In a phase II study of abiraterone plus prednisone in patients with CRPC and prior chemotherapy failure ($n = 58$), 50% PSA declines occurred in 55% of patients who were ketoconazole naïve, versus 30% of those who had received prior ketoconazole, and the median times to PSA progression were 198 days and 99 days, respectively [14]. Also, in a study of abiraterone plus prednisone in patients without prior chemotherapy or ketoconazole treatment ($n = 33$), a 50% PSA decline was achieved by 79% of patients and the median time to PSA progression was 71 weeks [15]. In a phase III randomized, double-blind, placebo-controlled trial of 1,195 metastatic CRPC patients previously treated with docetaxel, abiraterone plus prednisone led to a longer overall survival time than with treatment with prednisone plus placebo (median overall survival time, 14.8 versus 10.9 months; hazard ratio [HR], 0.65; $p < .0001$) [16]. A second phase III trial of abiraterone in asymptomatic or mildly symptomatic men with metastatic CRPC who had not received prior chemotherapy has completed accrual, with final results pending data maturity (Table 1).

TAK-700 is a novel CYP450c17 inhibitor similar to abiraterone. In preliminary data from a phase I/II study in patients with asymptomatic metastatic CRPC, TAK-700 was well tolerated and preliminary evidence of activity was seen, including 50% PSA declines in 12 of 15 patients who received doses ≥300 mg twice daily for ≥3 months [17].

Conversion of testosterone to the more potent DHT by 5α-reductase can occur within tumor tissue and is a mechanism for continued AR activation. Dutasteride, a dual-isoform 5α-reductase inhibitor, was evaluated in several phase II trials. In a study of 25 evaluable patients with asymptomatic CRPC, two had a confirmed 50% PSA decline and nine had stable disease (SD) for 2.5–9 months (defined by PSA, RECIST, bone scan, and symptomatic criteria) [18]. Dutasteride plus ketoconazole and hydrocortisone was also studied in 57 patients with CRPC, resulting in a 50% PSA response in 56% of patients and median time to progression (TTP) of 14.5 months [19]. If antitumor effects are to be seen with dutasteride, it is likely that a dose >0.5 mg/day used in benign prostatic hypertrophy will be required.

Paradoxically, preclinical studies have shown that testosterone, if given at a high enough dose, caused regression of an androgen-independent prostate cancer cell line [20]. In a prior phase I trial of exogenous testosterone administered at three times the normal dose to 12 men with CRPC, treatment was well tolerated, and a >50% PSA decline was observed in one patient [21]. In order to block peripheral conversion to DHT and potentially increase serum testosterone levels and the therapeutic effect, dutasteride was added to high-dose exogenous testosterone and is currently being studied in an ongoing phase II trial.

HE3235, a structurally related synthetic analog of androstenediol, an adrenal androgen, has shown preclinical activity against CRPC cells and xenografts. In preclinical models of LNCaP cell lines exposed to the combination of HE3235 and either DHT or androstenediol, there was greater AR activity and PSA expression. Parodoxically, however, the addition of HE3235 led to inhibition of tumor formation/growth in xenograft studies, likely through inducing a proapoptotic effect on tumor cells [22]. Phase I studies have determined that HE3235 is well tolerated across a range of doses, and phase II studies are under way [23].

Targeting Non–AR-Mediated Signaling

In addition to AR-mediated pathways, evidence suggests that several alternative signaling pathways may also be involved in prostate cancer disease progression. Whether or

Table 1. Selected ongoing clinical trials of targeted agents in CRPC

Target	Agent	Phase	Design	Population	Primary endpoint	Estimated *n* of patients	ClinicalTrials.gov identifier
Androgen synthesis (CYP17)	Abiraterone and prednisone	III	Randomized, placebo controlled	Metastatic CRPC after docetaxel failure	OS	1,158	NCT00638690
	Abiraterone and prednisone	III	Randomized, placebo controlled	Asymptomatic or mildly symptomatic CRPC	OS, PFS	1,000	NCT00887198
	Abiraterone and prednisone	II	Single arm	Metastatic CRPC	Hormonal effects	60	NCT00544440
	TAK-700	II	Single arm	Chemotherapy-naïve nonmetastatic CRPC	PSA	42	NCT01046916
	TAK-700	I/II	Dose ranging	Chemotherapy-naïve metastatic CRPC	Safety	100	NCT00569153
	TAK-700 plus docetaxel and prednisone	I/II	Dose ranging	Chemotherapy-naïve metastatic CRPC	MTD, PK, PSA response	40	NCT01084655
5α-reductase	Dutasteride plus testosterone	II	Single arm	Metastatic CRPC	PFS	30	NCT00853697
Androgen analog (androstenediol)	HE3235	I/II	Dose ranging	Metastatic CRPC after taxane failure	Safety, PK, activity	122	NCT00716794
Androgen receptor	MDV3100	III	Randomized, placebo controlled	CRPC after docetaxel failure	OS	1,200	NCT00974311
	MDV3100	III	Randomized, placebo controlled	Chemotherapy-naïve metastatic CRPC	OS, PFS	1,680	NCT01212991
BCL-2, BCL-XL, MCL-1	AT-101 and docetaxel	II	Randomized, placebo controlled	Chemotherapy-naïve metastatic CRPC	OS	220	NCT00571675
Clusterin (chaperone protein)	Custirsen plus docetaxel and prednisone	III	Randomized, placebo controlled	Chemotherapy-naïve CRPC	OS	800	(Planned)
	Custirsen plus docetaxel and prednisone	III	Randomized, placebo controlled	Metastatic CRPC after docetaxel failure	Pain palliation	292	NCT01083615
CTLA-4	Ipilimumab	III	Randomized, placebo controlled	Metastatic CRPC after docetaxel failure	OS	800	NCT00861614
	Ipilimumab	III	Randomized, placebo controlled	Asymptomatic or mildly symptomatic CRPC	OS	600	NCT01057810
Endothelin A receptor	Atrasentan plus docetaxel and prednisone	III	Randomized, placebo controlled	Chemotherapy-naïve metastatic CRPC	OS, PFS	930	NCT00134056
	Zibotentan	III	Randomized, placebo controlled	Chemotherapy-naïve nonmetastatic CRPC	OS, PFS	1,500	NCT00626548
	Zibotentan	III	Randomized, placebo controlled	Asymptomatic or mildly symptomatic CRPC with bone metastases	OS	848	NCT00554229
	Zibotentan plus docetaxel	III	Randomized, placebo controlled	Chemotherapy-naïve metastatic CRPC	OS	1,445	NCT00617669
IGF-1R	Cixutumumab plus mitoxantrone and prednisone	II	Randomized, open label versus IMC-1121B	Metastatic CRPC after failure on docetaxel-based chemotherapy	PFS	132	NCT00683475
	Figitumumab plus docetaxel and prednisone	II	Single arm	Chemotherapy-naïve or docetaxel-refractory CRPC	PSA, tumor response	120	NCT00313781
IGF-1R, mTOR	Cixutumumab plus temsirolimus	I/II	Single arm	Chemotherapy-naïve metastatic CRPC	Tumor response, time to progression	48	NCT01026623
mTOR	Everolimus	II	Single arm	Metastatic or locally advanced CRPC that is not progressing rapidly	PFS	39	NCT00976755
	Everolimus plus docetaxel and prednisone	I/II	Single arm	Metastatic CRPC	Safety, tumor response	60	NCT00459186
	Everolimus plus bicalutamide	II	Randomized, placebo controlled	Metastatic or recurrent CRPC	PSA response	80	NCT00814788
	Everolimus	II	Molecular, genetic, and genomic assessments of mTOR inhibition	Metastatic CRPC	mTOR inhibition	60	NCT00636090
	Temsirolimus	II	Single arm	Chemotherapy-naïve CRPC	Tumor response	24	NCT00919035
	Ridaforolimus plus bicalutamide	II	Randomized, placebo controlled	Asymptomatic metastatic CRPC	PSA response, dose-limiting toxicities	156	NCT00777959

(continued)

Table 1. (Continued)

Target	Agent	Phase	Design	Population	Primary endpoint	Estimated *n* of patients	ClinicalTrials.gov identifier
mTOR, VEGF	Temsirolimus plus bevacizumab	I/II	Dose ranging	Metastatic CRPC after chemotherapy failure	MTD, composite response	34	NCT01083368
RANKL	Denosumab	III	Randomized, placebo controlled versus zoledronic acid	CRPC with bone metastases	Time to skeletal-related event	1,904	NCT00321620
	Denosumab	III	Randomized, placebo controlled	Nonmetastatic CRPC	Time to bone metastasis	1,435	NCT00286091
Src	Dasatinib plus docetaxel and prednisone	III	Randomized, placebo controlled	Chemotherapy-naïve metastatic CRPC	OS	1,380	NCT00744497
	Dasatinib or nilutamide	II	Genomic-guided therapy	Metastatic CRPC	PFS	60	NCT00918385
	Saracatinib	II	Randomized versus zoledronic acid	Recurrent or progressive prostate or breast cancer with bone metastases	Bone markers	132	NCT00558272
VEGF	Bevacizumab plus docetaxel and prednisone	III	Randomized, placebo controlled	Chemotherapy-naïve CRPC	OS	1,020	NCT00110214
	Bevacizumab plus lenalidomide plus docetaxel and prednisone	II	Single arm	Metastatic chemotherapy-naïve CRPC	Safety	57	NCT00942578
	Aflibercept (VEGF trap) plus docetaxel and prednisone	III	Randomized, placebo controlled	Metastatic chemotherapy-naïve CRPC	OS	1,200	NCT00519285
VEGFR	Cediranib	II	Single arm	Metastatic chemotherapy-naïve CRPC after docetaxel failure	PFS	62	NCT00436956
	Cediranib plus docetaxel and prednisone	II	Randomized versus docetaxel/prednisone	Chemotherapy-naïve CRPC	PFS	104	NCT00527124
VEGFR, PDGFR, Kit	Sunitinib plus prednisone	III	Randomized, placebo controlled versus prednisone	Metastatic CRPC after docetaxel failure	OS	819	NCT00676650
	Sunitinib	II	Single arm	Metastatic CRPC after docetaxel failure	PFS	50	NCT00748358
VEGFR, PDGFR, RAF, Kit	Sorafenib plus docetaxel	II	Single arm	Metastatic chemotherapy-naïve CRPC	PSA response	69	NCT00589420

Abbreviations: BCL, B-cell lymphoma; CTLA-4, cytotoxic T-lymphocyte antigen 4; CRPC, castration-resistant prostate cancer; CYP, cytochrome P450; IGF-1R, insulin-like growth factor-1 receptor; MCL-1, myeloid cell leukemia sequence 1; MTD, maximum-tolerated dose; mTOR, mammalian target of rapamycin; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PK, pharmacokinetics; PSA, prostate-specific antigen; RANKL, receptor activator for nuclear factor κB ligand; VEGFR, vascular endothelial growth factor receptor.

not these pathways are truly independent of the AR or downstream components of AR signaling has not been fully elucidated, but this may vary by pathway. Several pathways that are a current focus for research with targeted agents are discussed below (Fig. 2).

Src Pathway

Src and other members of the Src-family kinases (SFKs) are nonreceptor tyrosine kinases that transduce signals from a range of upstream proteins, including receptors for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) [24]. In addition to the established role of growth factor receptors in prostate cancer oncogenesis, preclinical studies have shown that Src and SFKs are highly active and/or overexpressed during prostate tumor growth and metastasis [25]. Src is also required during osteoclast functioning [26]. In a recent study of tumor samples from patients with CRPC, SFK activity was elevated in approximately 30% of cases and patients with greater SFK activity had a significantly shorter overall survival duration [27].

Dasatinib is a potent inhibitor of Src and SFKs that has shown preclinical antitumor and antimetastatic activity against prostate cancer cells and antiosteoclast activity [28–31]. In a phase II trial of dasatinib monotherapy in 47 patients with metastatic chemotherapy-naïve CRPC, 6% had a 50% reduction in PSA, 12 of 23 patients (52%) with RECIST-evaluable disease had SD, and 23 of 41 patients (49%) with bone metastases at baseline had no new bone lesions at week 12 [32]. In a phase I/II study of dasatinib plus docetaxel and prednisone in chemotherapy-naïve patients with CRPC, 49% had a 50% PSA decline and 58% of

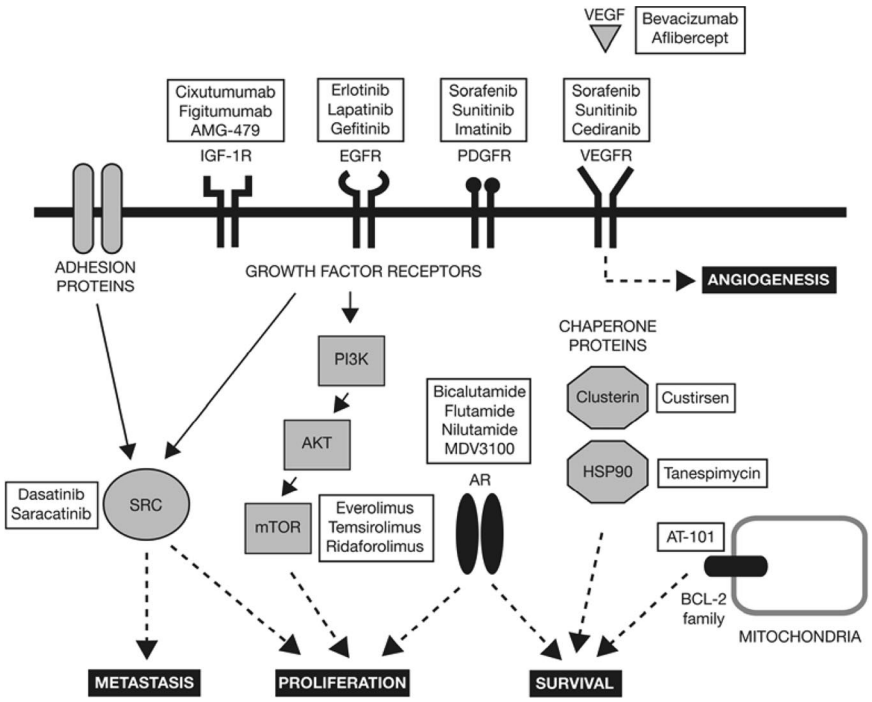

Figure 2. Molecular targets of agents being investigated for the treatment of castration-resistant prostate cancer.

Abbreviations: AR, androgen receptor; BCL-2, B-cell lymphoma 2; EGFR, epidermal growth factor receptor; HSP90, heat-shock protein 90; IGF-1R, insulin-like growth factor-1 receptor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide-3-kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGFR receptor.

evaluable patients had a RECIST PR. Bone scans showed a reduction in the size and/or number of lesions in 28% of patients and no new lesions in 69% of patients [33]. These findings led to a randomized, placebo-controlled phase III trial of dasatinib plus docetaxel.

Saracatinib (AZD0530) is another oral Src inhibitor in clinical development. In preclinical studies, saracatinib blocked proliferation and migration in a range of prostate cancer cell lines, including androgen-independent xenografts [34–36]. Saracatinib has also shown antiosteoclast activity in vitro and in vivo [37, 38]. In an initial phase II, single-arm, Simon two-stage trial of saracatinib monotherapy in patients with advanced CRPC, five of 28 patients had a slight decline in PSA, though no patient achieved a 30% decline. The median progression-free survival interval was 8 weeks [39].

Phosphoinositide-3-Kinase–Akt–Mammalian Target of Rapamycin Pathway

Upregulation of the phosphoinositide-3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) pathway has been detected in various tumors, including prostate cancer [40]. PI3K is activated by several extracellular receptors, including EGF receptor and insulin-like growth factor-1 receptor (IGF-1R), in addition to intracellular oncogenes such as *RAS* [41]. In turn, activated PI3K induces Akt to phosphorylate and activate mTOR, which promotes cell division. PI3K activation is regulated by tumor suppressor phosphatase and tensin homolog (PTEN), and loss of PTEN function has been detected in prostate cancer [42–44]. Preclinical studies suggest that loss of PTEN function and/or activation of the PI3K–Akt–mTOR pathway can result in androgen-independent prostate cancer growth [45, 46]. Furthermore, deletion of *PTEN* has been associated with earlier disease progression in patients with prostate cancer [47, 48] and greater AR expression and cancer-associated mortality in patients with CRPC [49].

Several mTOR inhibitors have been developed. In mouse studies, everolimus (RAD001) inhibited the growth of prostate cancer cells in bone and effects were augmented by combination treatment with docetaxel and zoledronic acid [50]. In a phase I dose-escalation trial of everolimus plus docetaxel in chemotherapy-naïve patients with metastatic CRPC and a positive fluorodeoxyglucose positron emission tomography scan, there were no dose-limiting toxicities. Of 14 evaluable patients, 10 had metabolic SD and four had a metabolic PR [51]. In a phase I trial of everolimus plus docetaxel and bevacizumab in patients with metastatic, chemotherapy-naïve CRPC, 50% PSA declines were seen in 10 of 12 patients [52]. In a phase II,

single-arm, Simon two-stage study of everolimus monotherapy in 19 patients with CRPC, most of whom were docetaxel refractory, the median TTP was 85 days and no PSA or tumor responses were recorded [53]. In preclinical studies, temsirolimus (CCI-779) inhibited the growth of prostate cancer cell lines and xenografts, and had greater activity in combination with docetaxel [54, 55]. In addition, phase I studies of ridaforolimus (AP23573) in patients with advanced solid tumors have successfully been completed [56, 57]. A single-arm, phase II trial of ridaforolimus monotherapy in taxane-resistant CRPC patients has completed enrollment and results are pending (ClinicalTrials.gov Identifier, NCT00110188). Clinical studies with everolimus, temsirolimus, and ridaforolimus in CRPC are summarized in Table 1.

Chaperone Proteins

Chaperone (heat-shock) proteins have antiapoptotic properties and are an established target for anticancer therapy. Although heat-shock protein 90 (HSP90) was an early focus for study, no HSP90 inhibitor has so far proved to be therapeutically viable for prostate cancer, although work is ongoing [58]. Clusterin, an alternative chaperone protein, is a novel target. In prostate cancer cell lines, clusterin overexpression resulted in androgen-independent growth [59] and clusterin gene silencing induced apoptosis and significantly reduced growth [60]. Clusterin expression is upregulated in patients with prostate cancer who have received androgen-deprivation therapy (ADT) [61].

Custirsen (OGX-011) is an antisense inhibitor of clusterin that suppresses clusterin expression in tumor tissue when administered to patients with localized prostate cancer [62]. In vitro, custirsen was found to resensitize docetaxel-refractory prostate cancer cell lines to docetaxel [63]. A randomized phase II study of docetaxel plus prednisone with or without custirsen in patients with metastatic CRPC ($n = 82$) has been completed, and showed a longer median overall survival time in the custirsen arm (24 months versus 17 months; HR, 0.61; $p = .06$), although rates of PSA and tumor response were similar [64]. Based on these findings, phase III trials of OGX-011 plus docetaxel and prednisone are planned.

IGF-1R Pathway

IGF-1R has antiapoptotic and transforming activities, and IGF-1R–mediated signaling can be detected during several stages of metastasis, including adhesion, migration, and invasion [65]. In vitro models suggest that increased IGF-1R expression in prostate cancer cells can lead to androgen independence [66, 67]. In a recent study using frozen tissue specimens, IGF-1R was more frequently expressed in stromal tissue surrounding malignant than surrounding nonmalignant tissue and in high-grade than in low-grade tumors [68]. Studies of IGF-1R ligands have provided further evidence for the oncogenic role of IGF signaling. In transgenic mice expressing human IGF-1 in the basal prostate epithelium, spontaneous tumorigenesis was seen [69]. In a study of prostatic tumor tissue, expression of IGF-1 and IGF-2 was higher in high-grade than in low-grade tumors [70]. Furthermore, in a meta-analysis of clinical studies, elevated circulating concentrations of IGF-1 were associated with a greater risk for prostate cancer [71].

Three monoclonal antibodies against IGF-1R, cixutumumab (IMC-A12), figitumumab (CP-751,871), and AMG-479, are being assessed in CRPC patients and have demonstrated good tolerability in phase I studies [72–75]. In a phase II study of cixutumumab in men with asymptomatic metastatic CRPC, nine of 31 patients achieved SD for ≥6 months (range, 7.4–12.5 months) [76]. Further studies of IGF-1R antibodies are in progress (Table 1). The development of figitumumab was suspended after an unexpected finding of a higher treatment-related mortality rate when this agent was added to standard chemotherapy.

VEGF

VEGF, stimulated by such factors as hypoxia, low pH, and growth factor receptors, plays a key role in promoting angiogenesis and tumor progression in various tumor types. VEGF expression has been found in both localized and metastatic prostate cancer specimens, and higher plasma VEGF levels have been correlated with disease severity [77] In preclinical models, antibodies directed against VEGF inhibited the growth of prostate cancer tumors [78].

Bevacizumab, a humanized monoclonal antibody directed against VEGF, has been evaluated in prostate cancer in several clinical trials. In a phase II trial of 15 patients with CRPC, after 12 weeks of therapy with bevacizumab dosed at 10 mg/kg every 2 weeks, no patients experienced an objective response or PSA decline >50% [79]. In a randomized, double-blind, placebo-controlled phase III trial of docetaxel plus prednisone with or without bevacizumab in 1,050 men with chemotherapy-naïve CRPC, the median overall survival time was not significantly longer with the addition of bevacizumab; however, the median progressive-free survival interval was longer—7.5 months in the control arm and 9.9 months in the bevacizumab-containing arm (stratified log-rank p-value <.0001) [80].

Aflibercept, a VEGF trap consisting of the Fc portion of human IgG_1 fused to the extracellular ligand-binding domain of VEGF receptor (VEGFR)-1 and VEGFR-2, is currently being evaluated in a placebo-controlled, randomized

phase III trial in combination with docetaxel plus prednisone (ClinicalTrials.gov Identifier, NCT00519285).

Sunitinib, a small molecular tyrosine kinase inhibitor of VEGFR-1 to VEGFR-3, along with multiple other receptors including PDGF receptor (PDGFR)-α and PDGFR-β, inhibits angiogenesis and has shown promising activity in prostate cancer, especially in the postdocetaxel setting. In a single-arm, phase II trial of sunitinib in 36 men with metastatic CRPC previously treated with docetaxel, seven patients (21.2%) had a PSA decline >30% and two patients had an objective response [81]. A phase III trial, however, of sunitinib plus prednisone versus placebo plus prednisone, in men with CRPC and prior docetaxel and with a primary endpoint of overall survival, was terminated prematurely as a result of futility in September 2010 (ClinicalTrials.gov Identifier, NCT00676650).

Endothelin

The endothelin family of peptides, mediated mostly by endothelin-1 binding to the endothelin-A receptor, modulates vasomotor tone, nociception, and cellular proliferation in a variety of tissues [82]. Endothelin-1 acts via the endothelin-A receptor to promote prostate cancer progression via several mechanisms, including acting as a mitogen for both prostate cancer cells and osteoblasts, which are responsible for the osteoblastic metastatic lesions common in metastatic prostate cancer [83, 84]. Selective endothelin-A receptor antagonists block the proliferation of prostate cancer cells and osteoblasts in the presence of exogenous endothelin [84].

Atrasentan is a potent and highly selective inhibitor of the endothelin-A receptor, and was shown in a randomized phase II trial, at a dose of 10 mg/day, to produce a trend towards a longer TTP than with placebo in a study of 288 men with metastatic CRPC (median TTP, 183 days versus 137 days; $p = .13$) [85]. However, two subsequent, randomized, placebo-controlled, phase III trials of men with either nonmetastatic or metastatic CRPC failed to demonstrate a significantly longer time to disease progression in patients treated with atrasentan than in those treated with placebo [86, 87]. A randomized phase III trial comparing prednisone plus docetaxel with or without atrasentan has finished accrual, with final results pending (ClinicalTrials.gov Identifier, NCT00134056).

Zibotentan is a nonpeptide, orally bioavailable selective inhibitor of endothelin-A receptor that was well tolerated in a phase I trial, with a maximum-tolerated dose of 15 mg/day [88]. In a randomized, phase II trial with three treatment arms consisting of men with metastatic CRPC treated with zibotentan 10 mg/day, zibotentan 15 mg/day, or placebo, the primary endpoint of a longer time to disease progression was not significant; however, there was a trend toward longer overall survival in both zibotentan arms, compared with placebo, with a median follow-up of 22 months (HR, 0.76; $p = .103$ for the 15-mg arm. HR, 0.83; $p = .254$ for the 10-mg arm) [89]. Based on these results, three phase III trials of zibotentan in men with CRPC are ongoing (Table 1).

Individualized Targeted Therapy for CRPC

Individual Tumor Gene/Protein Expression to Guide Therapy

Because of biological heterogeneity, including the potential for continuing AR-mediated signaling or androgen independence, it is likely that no single agent will be uniformly effective for treating CRPC. This hypothesis is supported by the variable efficacy observed in clinical trials of the selected novel agents outlined above. A more individualized and arguably more rational approach to treatment is currently being investigated in CRPC, which involves using genomic and proteomic analyses to assess the involvement of specific molecular pathways. The aim is to tailor treatment based on individual tumor characteristics and thereby select patients who are most likely to respond to different therapies. The benefits of individualized therapy have already been demonstrated in other tumor types, particularly in breast cancer using human epidermal growth factor receptor 2 testing and trastuzumab therapy. Predictive markers of response to secondary hormonal therapy in CRPC have already been identified. For example, CRPC tumors with *AR* gene amplification respond better to secondary hormone therapy (combined androgen blockade) than tumors without *AR* amplification [90].

Recent studies in CRPC have further evaluated a genomic-guided approach to treatment [91]. Using an androgen-sensitive prostate cancer cell line (LNCaP), a transcription signature for AR activity was identified, which was confirmed to be robust in independent data sets of prostate cancer cell lines and human tumors. When the AR signature was investigated in patient samples, AR activity was generally higher in localized, untreated tumors and lower after neoadjuvant hormone therapy and in CRPC, seemingly representing declining AR activity with prostate cancer progression. However, AR activity was heterogeneous in CRPC patients, with approximately one third of patient samples showing persistent AR activity, which could help to explain the variable responses to AR-directed therapies observed in trials. To identify novel therapeutic options that may be most useful for patients with low AR activity, samples were compared with published signatures for other molecular targets [91–93]. Of those tested, the signature for Src activity most consistently correlated with low AR activity, both in localized ($p = .0071$) and metastatic ($p = .0033$) disease. Similarly, low AR activity correlated with a signal predicting sensitivity to the Src inhibitor dasatinib ($p = .019$).

These findings suggest that patients with CRPC who have low AR activity detected in tumor samples might benefit more from Src inhibitor treatment than AR-directed therapy.

A prospective study is now in progress to test a genomic-guided approach to treatment (ClinicalTrials.gov Identifier, NCT00918385). Patients with metastatic CRPC will be prescreened and those with tumors with high AR activity will receive nilutamide, an AR-targeted agent, whereas those with low AR activity will be treated with dasatinib. Patients failing single-agent treatment will receive combination therapy. A study is also being performed with everolimus that will examine gene expression profiles and molecular characteristics in patients with CRPC to determine any possible association with treatment responses, which could potentially inform a future genomic-guided trial (ClinicalTrials.gov Identifier, NCT00636090).

A key question in the development of genomic-guided clinical trials centers around the type of specimen that is used to molecularly define an individual patient's tumor. Prior comprehensive gene expression analyses that compared localized prostate cancers with metastatic tumors found wide variability in the expression of various subsets of genes, including those involved in cell cycling, cell adhesion, and signal transduction [94]. Given the molecular heterogeneity of prostate cancer, there has been considerable interest in developing techniques to molecularly characterize metastatic prostate cancer tissue rather than specimens obtained from prior prostate biopsies or prostatectomy specimens containing localized prostate cancer. In the aforementioned phase II trial of nilutamide and dasatinib (ClinicalTrials.gov Identifier, NCT00918385), fresh tissue obtained via biopsy of a metastatic site will be used to molecularly characterize a patient's tumor.

Circulating tumor cells (CTCs) potentially represent an alternative, less invasive means to obtain gene expression data. Techniques to identify and isolate these cells with increasing sensitivity and purity are actively being refined [95]. Enumeration of the number of CTCs pre- and postinitiation of chemotherapy was shown to be predictive of overall survival in a prospective study [96]. Needed, however, are refinements in techniques used to not only count, but also to characterize, CTC gene expression profiles, as well as studies that compare molecular profiles among CTCs, primary tumor samples, and metastatic sites within individual patients to assess for concordancy (or lack thereof) in gene expression over time and location.

Pharmacogenetic Profiling

Recent data have established that pharmacogenomic factors, that is, genetic polymorphisms affecting proteins involved in drug metabolism or action, may play a role in determining response to targeted therapies, both in prostate cancer and other solid tumors. For example, among 529 patients undergoing ADT, polymorphisms in three separate genes involved in hormone synthesis (*CYP19A1*, *HSD3B1*, and *HSD17B4*) were significantly ($p < .01$) associated with a longer TTP, and best responses were observed in patients with more than one polymorphism [97]. Furthermore, survival on docetaxel in patients with CRPC has been associated with specific genotypes of *ABCB1* (encoding a drug efflux protein) and *CYP1B1* (encoding an enzyme involved in estrogen metabolism) [98, 99]. Tailoring therapy based on pharmacogenomic parameters is likely to be tested in future prospective studies.

Conclusions

Traditional drug discovery methods have identified several potential molecular targets for treating CRPC, including those that inhibit AR-mediated and non–AR-mediated signaling. In recent years, novel agents have shown promise in clinical trials, including agents targeting the androgen axis (e.g., novel AR antagonists and inhibitors of androgen production) and agents with other targets (e.g., Src, IGF-1R, mTOR, and clusterin). However, it is becoming increasingly apparent that CRPC is a heterogeneous disease and patient subgroups are likely to exist that are characterized by the involvement of different signaling pathways in disease progression to different degrees. This suggests that a more rational/individualized approach is required to maximize potential benefits from targeted therapy. Using genomic signatures, a recent study showed that patients with low AR activity are more likely to have high Src activity and sensitivity to dasatinib, and an ongoing study will provide an initial test of whether genomic-guided treatment can increase response rates. Identifying patient populations with a specific molecular subtype should hopefully improve the chances of treatment response, and ultimately, a scenario could be envisaged in which patients receive personalized targeted therapy based on their genomic profile, using both the "real-time" tumor genotype/phenotype and the pharmacogenetic profile of the patient. Discoveries in CRPC could translate to other advanced cancers.

Author Contributions

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